UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte BRIAN SEED and TARA POUYANI

Appeal 2007-0857
Application 08/756,018
Technology Center 1600

Decided: October 29, 2007

Before, TONI R. SCHEINER, DEMETRA J. MILLS, and NANCY J. LINCK, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for lack of written description. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Claim 10 is representative.

10. A purified nucleic acid encoding a polypeptide that is a synthetic P-selectin ligand, wherein said polypeptide contains an N-linked sialyl Le^x addition site and a tyrosine sulfation site, and wherein at least one of the sites is located at an amino acid position in said polypeptide which is different from its position in a naturally-occurring P-selectin ligand.

Grounds of Rejection[1]

Claims 10, 12-14, 24, and 25 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking written description in the Specification as filed.

References cited by Appellants

Hortin et al., *Characterization of Sites of Tyrosine Sulfation in Proteins and Criteria for Predicting Their Occurrence*, Biochem. Biophys, Res. Comm., Vol. 141, 326-333 (1986).

Huttner, Wieland B., *Tyrosine Sulfation and the Secretory Pathway*, Ann. Rev. Physiol., Vol. 50, 363-376 (1988).

DISCUSSION

Background

As background, the Specification describes that P-selectin is an integral membrane C-type lectin found within the Weibel-Palade bodies of endothelial cells. (Specification 1.) Once displayed on the cell surface, P-selectin supports the attachment of myelomonocytes to platelets or endothelial cells. (*Id.*) In this setting P-selectin heralds an underlying tissue insult and supports the initial step in leukocyte extravasation, and the rolling of neutrophils along the postcapillary venule wall. (*Id.* at 2.) A P-selectin ligand (PSGL), as defined in the Specification, is any amino acid sequence capable of mediating an interaction with the P-selectin receptor. (*Id.* at 5.)

Claim Interpretation

[1] A lack of enablement rejection of the claims has been withdrawn. Answer 4.

Claim 1 recites a purified nucleic acid encoding a polypeptide that is a synthetic P-selectin ligand, wherein said polypeptide contains an N-linked sialyl Le^x addition site and a tyrosine sulfation site, and wherein at least one of the sites is located at an amino acid position in said polypeptide which is different from its position in a naturally-occurring P-selectin ligand. As discussed above, according to the Specification, a P-selectin ligand is capable of mediating an interaction with the P-selectin receptor. (Specfication 5.) Further according to the Specification, a P-selectin ligand includes those proteins referred to as "P-selectin counter receptors". (Specfication 5.) The claimed P-selectin ligand has either a sialyl Le^x or tyrosine sulfation site at a position not found in wild type P-selectin ligand. The Specification defines "non-naturally occurring" as a sialyl-Le^x or sulfated determinant that is not one which is naturally bound to the molecule at that amino acid location. (*Id.* at 6.) An example of a "non-naturally occurring" portion of PSGL-1 or a site located at an amino acid position in said polypeptide which is different from its position in a naturally-occurring P-selectin ligand is a deletion mutant of the N-terminal portion of PSGL-1 which maintains P-selectin receptor binding. (Specification 7: 6-15.)

Written Description

Claims 10, 12-14, 24 and 25 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking written description in the Specification as filed.

The Examiner contends that the Specification discloses just a single functional example of a polypeptide as claimed. (Answer 4.) Thus, the Examiner argues that "one of skill in the art would therefore conclude that

the Specification fails to disclose a representative number of species to describe the claimed genus" of polypeptides that are synthetic P-selectin ligands. (*Id.*, at 3-4.) The Examiner particularly argues that the Specification fails to disclose sufficient limitations with regard to the location of the tyrosine sulfation sites and sialyl Le^x sites in relation to one another in a synthetic P-selectin ligand. (Final Rejection 4.)

"The 'written description' requirement [under 35 U.S.C. § 112, first paragraph,] implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005).

Moreover, "a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function." *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Instead, the written description must define the genus in a manner that enables one skilled in the art to "visualize or recognize the identity of the members of the genus," e.g., by providing a description of "structural features commonly possessed by members of the genus that distinguish them from others." *Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Thus, the issue becomes whether Appellants have defined the genus of polypeptides whose members are synthetic P-selectin ligands, wherein

each member contains an N-linked sialyl Le^x addition site and a tyrosine sulfation site, and wherein at least one of the sites is located at an amino acid position in said polypeptide which is different from its position in a naturally-occurring P-selectin ligand, in a manner sufficient to enable one skilled in the art to "visualize or recognize the identity of the members of the genus," e.g., by providing a description of "structural features commonly possessed by members of the genus that distinguish them from others."

The following questions are relevant to the issue noted above.

-Does the Specification describe representative examples and additional sialyl Lex sites other than F8/CD43, which the Examiner characterizes as the only example described in the Specification? (Answer 4.)

-Does the Specification describe representative examples and additional tyrosine sulfation sites other than F8/CD43, which the Examiner characterizes as the only example described in the Specification? (Answer 4.)

-Does the Specification describe representative examples where the two sites (sialyl Le^x and tyrosine sulfation) are positioned differently in relation to each other than in wild-type PSGL-1?

For the reasons discussed below, we find the Specification meets the written description requirement of 35 U.S.C. § 112, first paragraph.

As further background, in order to determine the portion of the PSGL-1 molecule responsible for P-selectin binding, Appellants created deletion mutants of the wild-type P-selectin ligand. (Specification 7-9.) Deletion mutants of PSGL-1 are shown in Figure 8A of the Specification.

(Specification 9.) Preferred P-selectin ligands contain tyrosine sulfation sites as set forth in Figure 8A of the Specification. Deletion studies with PSGL-1 showed that removal of the first 20 amino acids of the N-terminus of PSGL-1 did not affect P-selectin binding, however, amino acid residues 20 to 40 of PSGL-1 (residues 38 to 57 of the predicted precursor having the signal sequence) are required for P-selectin binding. (Specification 21.) Both sialyl Le^x and sulfated determinants are present on a P-selectin ligand consisting essentially of amino acids 21-57 of Fig 8A. (Specification 5.) A P-selectin ligand, according to the Specification, preferably includes at least one copy of a repeat sequence, ATEAQTTPPA or MATNSLETSTGTSGPPVT. (Specification 2.)

Does the Specification describe representative examples and additional sialyl Le^x sites other than F8/CD43?

The Examiner contends that "[t]he Specification discloses no limitation on the sites which might comprise a 'sialyl Le^x addition site'…". (Answer 3.) The Examiner argues that absent any disclosed limitations, a "sialyl Le^x addition site" must be considered to be any amino acid capable of accepting either an O-linked or N-linked carbohydrate addition. (Answer 3.)

Appellants contend that, contrary to the Examiner's assertion, a sialyl Le^x site cannot be any amino acid capable of accepting either an O-linked or N-linked carbohydrate addition, and point out that claim 10 is limited to N-linked sialyl Le^x addition sites. (App. Br. 17.) Appellants argue that the Specification describes that N-linked glycan addition sites occur at the consensus sequence of N X S/T, wherein N is asparagine, S is serine, T is

threonine and X is any amino acid except proline. (App. Br. 17.) As an example, Appellants argue that Figure 10 of the Specification identifies at least five sites for N-linked glycan addition in IgG1. (*Id.*) Appellants argue that preferable sialyl Le^x sites are present or created in the CH_2 region of an immunoglobulin molecule, and are located on the outside of the immunoglobulin or in a region which is minimally disruptive to the primary and secondary structure of the protein. (App. Br. 17-18; Specification 25, l. 22 to 26, l. 17.)

With respect to sialyl Le^x sites, Appellants further determined that in PSGL-1, specific sialyl Le^x sites are located at threonines at positions 44 and 57 and are required for P-selectin binding. (Specification 22, l. 24 to 23, l. 4.)

Appellants argue that the Specification demonstrates that a fusion protein of the N-terminal domain of PSGL-1, containing the tyrosine sulfation site, facilitates P-selectin binding activity in chimeric molecules having a sialyl Le^x site derived from CD43, CD34, or GlyCAM-1. (*Id.*) Appellant concludes that these experiments provide examples of various sialyl Le^x sites and "show that P-selectin binding is tolerant of considerable sequence variability in the region linking the tyrosine sulfation and the sialyl Le^x sites." (App. Br. 10.)

The Examiner does not respond to Appellants' arguments with respect to guidance to those of ordinary skill in the art regarding positioning and requirements of sialyl Le^x addition sites on molecules with P-selectin binding.

We find that not only does the Specification describe the exact location and spacing of sialyl Le^x sites in PSGL-1 (Specification 22), but the Specification also provides examples of at least three chimera of a portion of PSGL-1 combined with the sialyl Le^x sites of CD43, CD34, or GlyCAM-1. (Specification 7, l. 21 to 8, l.3.) Thus we find that the Specification describes various sialyl Le^x sites in addition to the one example noted by the Examiner.

Does the Specification describe representative examples and additional tyrosine sulfation sites other than F8/CD43?

The Examiner argues absent any disclosed limitations a "tyrosine sulfation site" must be considered to be any tyrosine. (Answer 3.) The Examiner concludes that "the claims would … encompass an essentially unlimited number of nucleic acids encoding an essentially unlimited number of polypeptides," and that Appellants have only provided a single example of a tyrosine sulfation site. (Answer 3, 6.)

Appellants argue that tyrosine sulfation occurs at tyrosines that are contained within sequences of a very special character and for which tests are available in the art. (App. Br. 18.) Appellants reference the prior art publications of Hortin and Huttner explaining five simple rules empirically derived to aid in predicting the location of sites of sulfation. (App. Br. 8.) Appellants specifically direct the Examiner's attention to the example of Figure 14 of the Specification which describes the tyrosine sulfation site of coagulation Factor VIII and the fourth component of human complement. Appellants further argue they have demonstrated the tolerance of PSGL-1

sulfation site to modification. (App. Br. 18.) Appellants point to Figure 9 and the Specification page 22 line 7 to page 23, line 4, providing experimental data on the biological effects of altering the tyrosine sulfation site of PSGL-1. They demonstrate that conversion of tyrosines to phenylalanines results in the complete loss of P-selecting binding, whereas replacement of threonine residues with alanine reduced but did not abolish binding activity. (App. Br. 18-19.) Appellants' data from experiments set forth in the Specification indicate that tyrosines at positions 46, 48 and 51 are required for P-selectin ligand binding activity. (Specification 22: 7-25.) Thus, the Specification provides information regarding the relative positioning of tyrosine sulfation sites in molecules which possess P-selectin binding.

Again, the Examiner has not addressed Appellants specific arguments regarding teachings in the Specification concerning requirements for tyrosine sulfation in P-selecting binding or the additional examples of tyrosine sulfation sites which Appellants have identified in the Specification. We find the Specification provides information regarding the structural features commonly possessed by tyrosine sulfations sites of synthetic polypeptides which function as synthetic P-selectin ligand.

Does the Specification describe examples where the two sites are positioned differently in relation to each other?

First, the Examiner argues that the "other constructs disclosed in the Specification comprise fragments of the naturally occurring P-selectin ligand PSGL-1 which would not meet the limitations of the claims." (Answer 5.) We disagree. We find that the deletion fragments of PSGL-1 which

maintain P-selectin binding constitute polypeptides wherein at least one of the sites is located at an amino acid position in said polypeptide which is different from its position in a naturally-occurring P-selectin ligand. (See e.g., Specification Figs. 2, 3A and 4.) The deletion mutants are not naturally-occurring P-selectin ligand.

Next, the Examiner contends that Appellants have not described sufficient combinations of sialyl Le^x addition sites and tyrosine sulfation sites in a proper 3-dimensional context such that the construct is capable of binding P-selectin. (Answer 5-6.)

Appellants contend that the Specification describes artificial P-selectin ligands that are combinations of sialyl Le^x sites and tyrosine sulfation sites derived from different molecules, citing Figure 3. (App. Br. 19.) Appellants argue that the examples of chimeric molecules depicted in Figure 3 have varied spacing between the two sites. (App. Br. 19.) We agree.

Figure 3B shows that COS cells expressing a synthetic P-selectin ligand that is a chimera of PSGL-1-NH2 and either CD43or CD34 possess P-selectin binding activity equal to COS cells expressing native PSGL-1. (App. Br. 11.) This Figure also shows that chimera of PSGL-1-NH2 and GlyCAM possess a binding activity of approximately 50% compared to native PSGL-1. (*Id.*)

The Specification further describes an example of a polypeptide meeting the claim limitations which is a construct that comprises the amino acids of SEQ ID NO:15 and SEQ ID NO:17. (Answer 4.) SEQ ID NO: 15 is a sequence from Factor VIII constituting the tyrosine sulfation sites of that

molecule. (Specification 16: ll. 5-15.) SEQ ID NO: 17 is the cognate sequence of CD43 containing sialyl Le^x sites. (Specification 7: 15-20.) The Specification further indicates specific residues within the amino terminal peptide of PSGL-1 that are required for P- selectin binding. (Specification 22.) In particular, Appellants' data indicate that tyrosines at positions 46, 48 and 51 are required for P-selectin ligand binding activity. (Specification 22: 7-25.) Appellants further determined that in PSGL-1, specific sialyl Le^x sites are located at threonines at positions 44 and 57 and are required for P-selectin binding. (Specification 22, l. 24 to 23, l. 4.) Thus the Specification provides information regarding the relative positioning of sialyl Lex sites and tyrosine sulfation sites to serve as a model for other synthetic polypeptides which possess P-selectin binding.

Appellants further contend that "Figure 4 of Applicants' Specification demonstrates that P-selectin binding function is maintained despite considerable deletion of the repeated elements of PSGL". (App. Br. 10.) Appellants argue that Figure 4 shows that mutants having deletion of 4-8 elements retained approximately 75% of the native binding activity of PSGL. (*Id.*)

In conclusion, we disagree with the Examiner's conclusion that the Specification only provides one example of a construct within the scope of the claims. As Appellants point out, they have used deletion mutants to determine the binding portion of PSGL-1 and have localized an important sequence within the N-terminal portion required for binding. Appellants have further determined the location of important residues required for P-selectin binding for both sulfation and sialyl Le^x addition sites. Figure 2b

evidences P-selectin binding by a deletion mutant of PSGL-1 and CD43. Figure 3A evidences the same deletion mutant of PSGL-1 combined with CD43 repeats, CD34 or GlyCAM-1 and shows that these molecules also possess P-selectin binding (Figure 3B). Figure 4B shows P selectin binding of 8 mutants of PSGL-1 having successive deletion of repeated elements. Figure 14 shows fusion proteins of the tyrosine sulfation sites of Factor VIII or the fourth component of human complement with CD43. In our view, the Specification provides one of ordinary skill in the art with ample information regarding requirements for representative compounds which have P-selectin binding. The Specification provides the exact location and positioning of the tryrosine sulfation and sialyl Le^x addition sites of PSGL-1 and evidences several fusion proteins which also possess P-selectin binding.

In view of the above, we find the Specification as filed complies with the written description requirement of 35 U.S.C. § 112, first paragraph, and would have enabled one skilled in the art to "visualize or recognize the identity of the members of the genus," e.g., by providing a description of "structural features commonly possessed by members of the genus that distinguish them from others."

SUMMARY

The rejection of claims 10, 12-14, 24, and 25 under 35 U.S.C. § 112, first paragraph as lacking written description in the Specification as filed, is reversed.

REVERSED

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